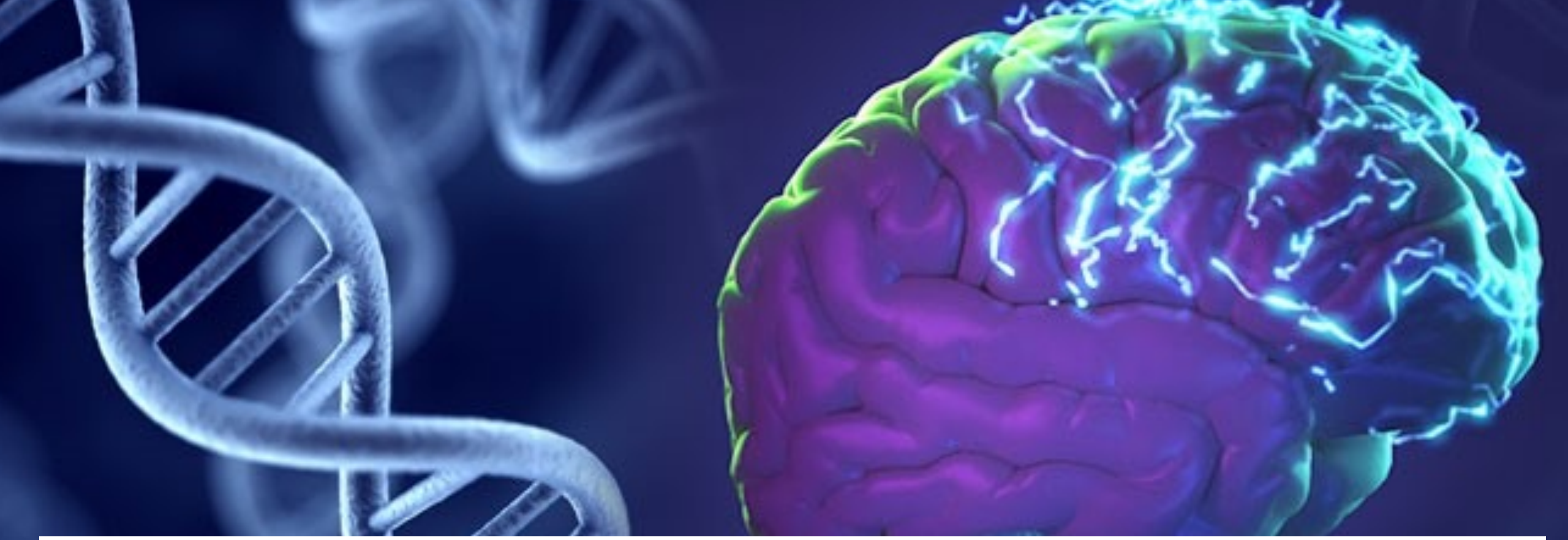

Is Precision Medicine The Answer to Developmental and Epileptic Encephalopathies (DEE)?

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Disclosure

- No financial disclosure
- The videos are used for educational purpose only

Precision Medicine (PM)

- A treatment that is targeted to the needs of individual patients on the basis of genetic, biomarker, phenotypic, psychological characteristics that distinguish a given patient from other patients with similar clinical presentations

- Clinical implications: e.g., duration of treatment, impact on neurodevelopment (if early treatment)

Jameson HL, NEJM 2015

Developmental Epileptic Encephalopathies (DEE)

- **DEE**: Diseases have developmental impairment related to both the underlying etiology independent of epileptiform acitivity and the epileptic encephalopathy

- **Epileptic encephalopathy (EE):** epileptic activity itself is postulated ot contribute ot developmental impairment

- **Developmental encephalopathy**: developmental delay or intellecutal disability, representing a static disability although the degree of disability may become more evident with age

Scheffer I, Eur J Paediatr Neurol 2020

Developmental Epileptic Encephalopathies (DEE)

Self-limited epilepsies

- Self-limited neonatal epilepsy (SeLNE)
- Self-limited familial neonatal-infantile epilepsy (SeLFNIE)
- Self-limited infantile epilepsy (SeLIE)
- Genetic epilepsy with febrile seizures plus (GEFS+)
- Myoclonic epilepsy in infancy (MEI)

Developmental and epileptic encephalopathies (DEE)

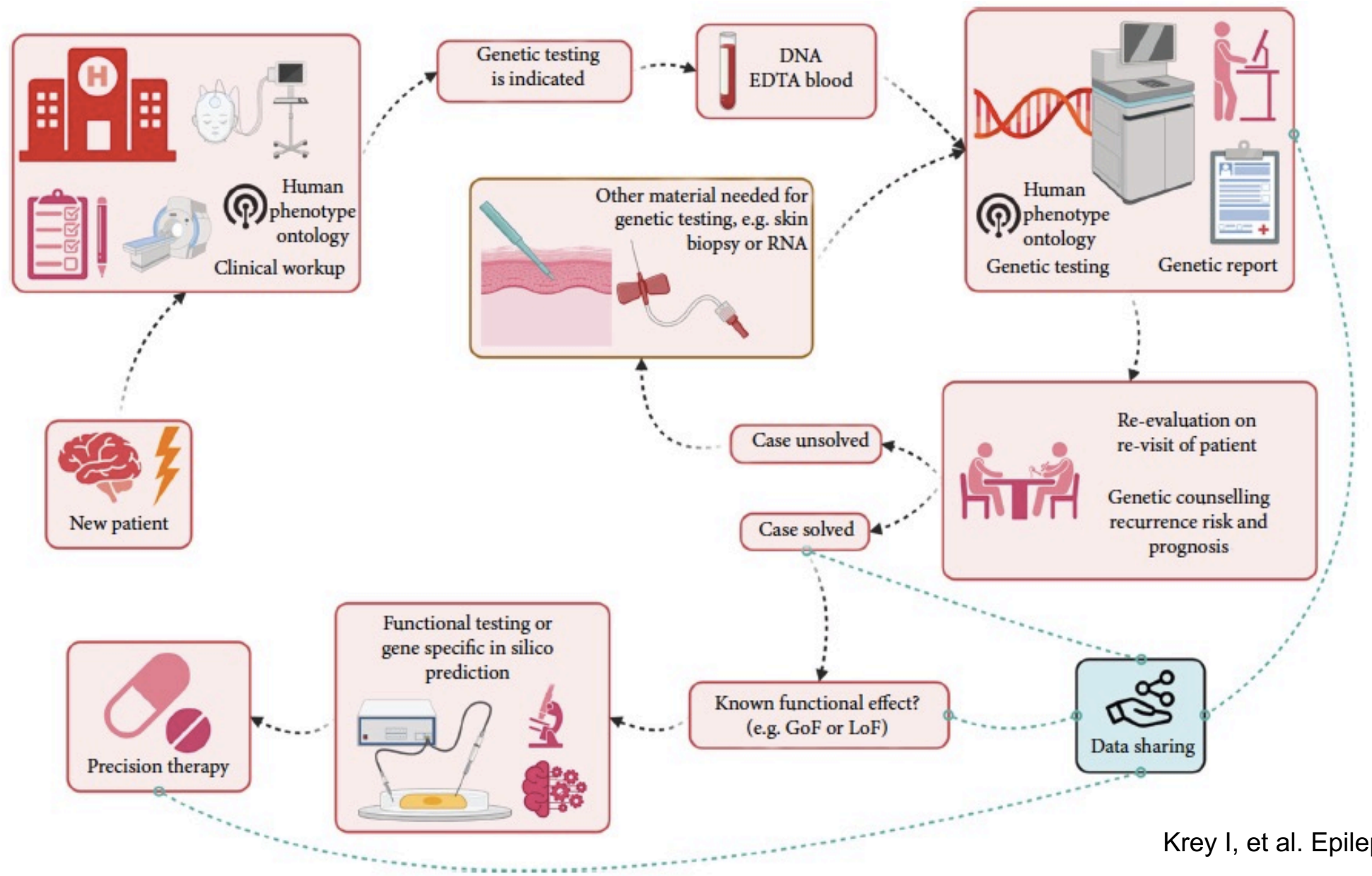
- Ealy infantile developmental and epileptic encephalopathy (EIDEE)
- Epilepsy in infancy with migrating focal seizures (EIMFS)
- Infantile epileptic spasms syndrome (IESS)
- Dravet syndrome (DS)

Etiology-specific syndromes

- *KCNQ2*-DEE
- Pyridoxine-dependent (*ALDH7A1*)-DEE (PD-DEE)
- Pyridox(am)ine 5'-Phosphate Deficiency (PNPO)-DEE (P5PD-DEE)
- *CDKL5*-DEE
- *PCDH19* clustering epilepsy
- Glucose Transporter 1 Deficiency Syndrome (GLUT1DS)
- Sturge Weber syndrome (SWS)
- Gelastic seizures with hypothalamic hamartoma (GS-HH)

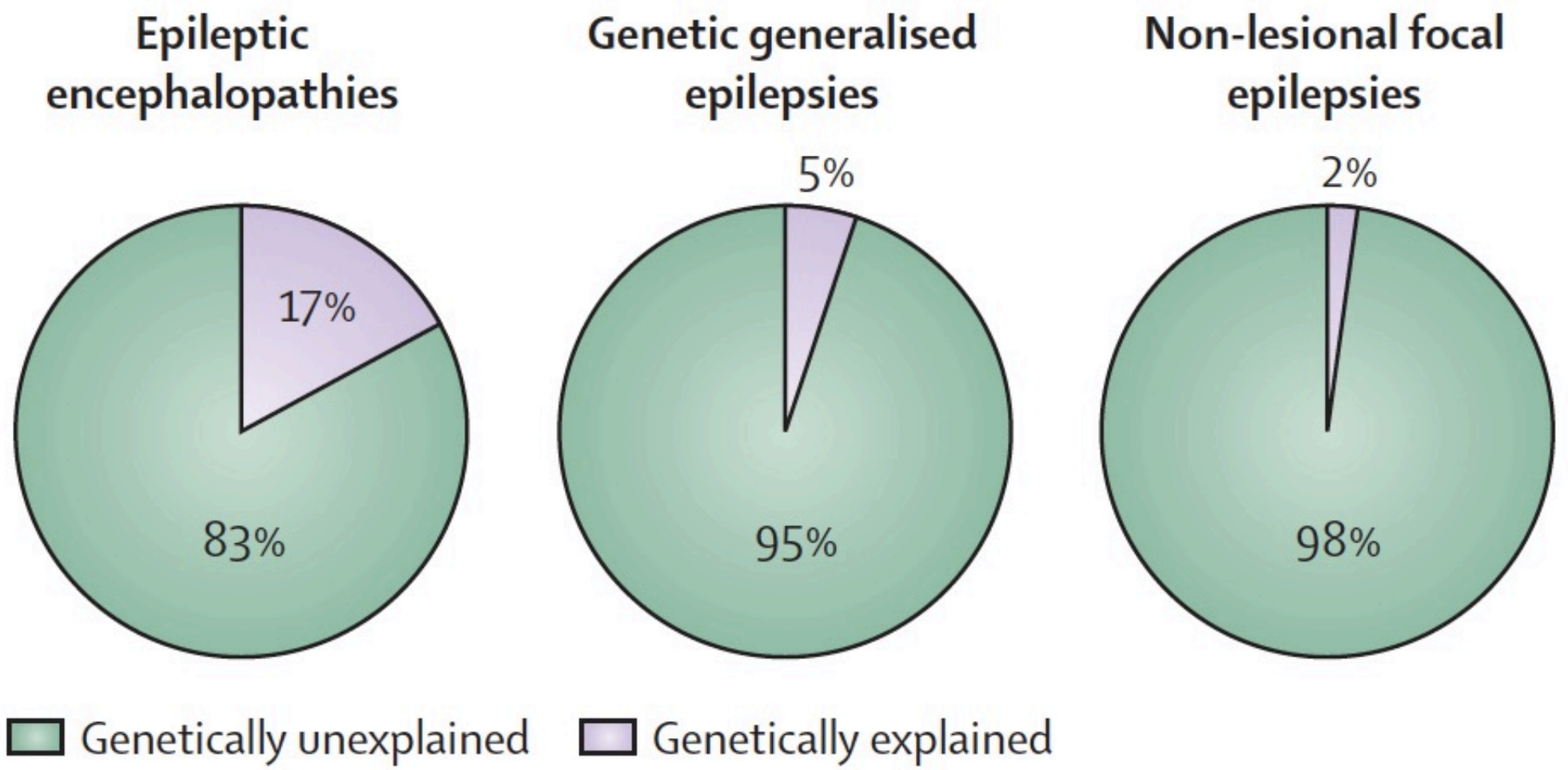
Zuberi M, ILAE Task Force 2022

Workflow of Genetic Testing



Krey I, et al. Epileptic Disord 2022

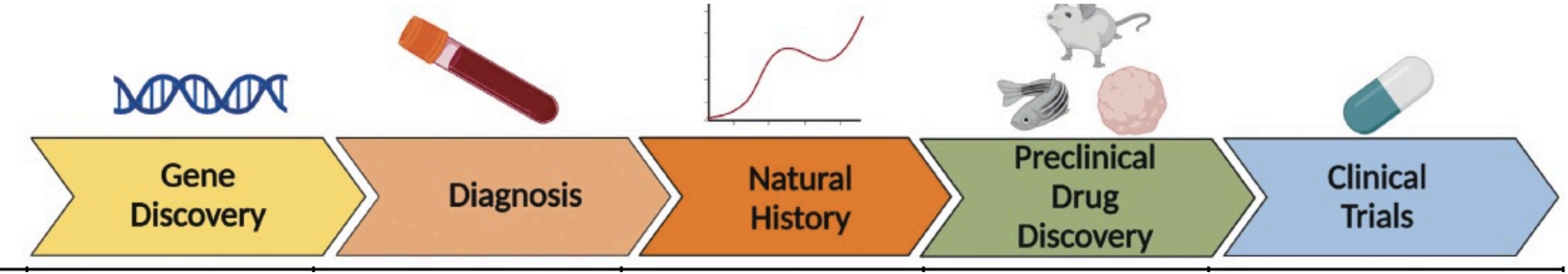
Proportion of Genetically Explained Epilepsy



Likelihood of identifying a genetic cause decreases with increasing age at onset of the epilepsy

EpiPM Consortium, Lancet Neurol 2015

PM for Genetic Epilepsy: Overview



Knowles JK et al. Epilepsia 2022

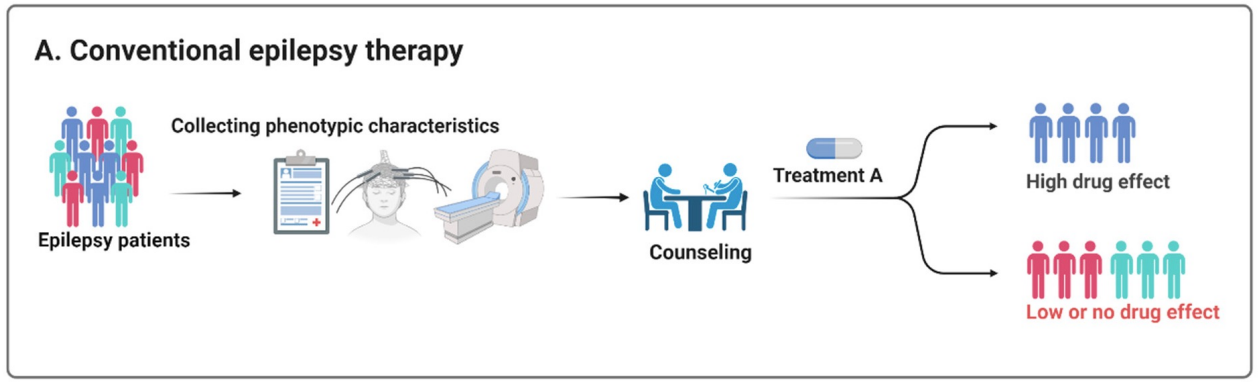
Treatment Paradigm Shift

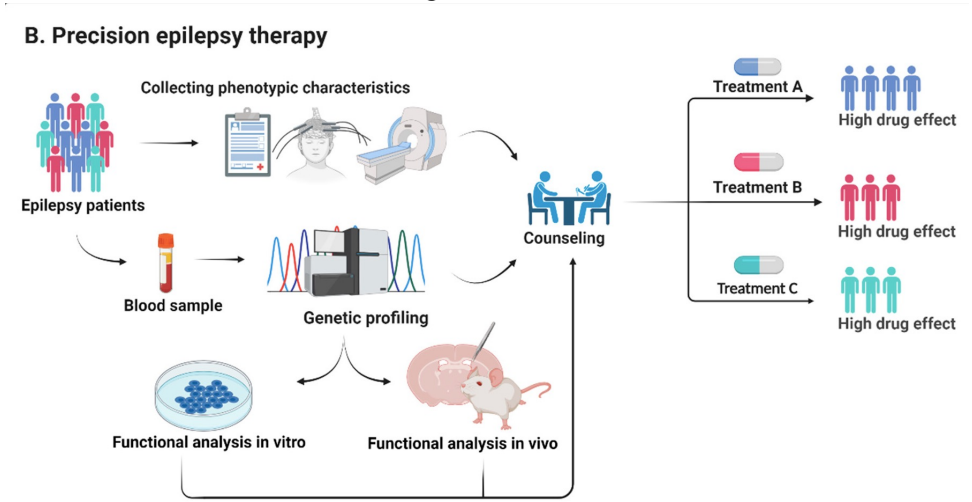
Reactive Approach
‘One-size-fits-all’

- Identify electroclinical syndrome
- Treat after the onset of epilepsy

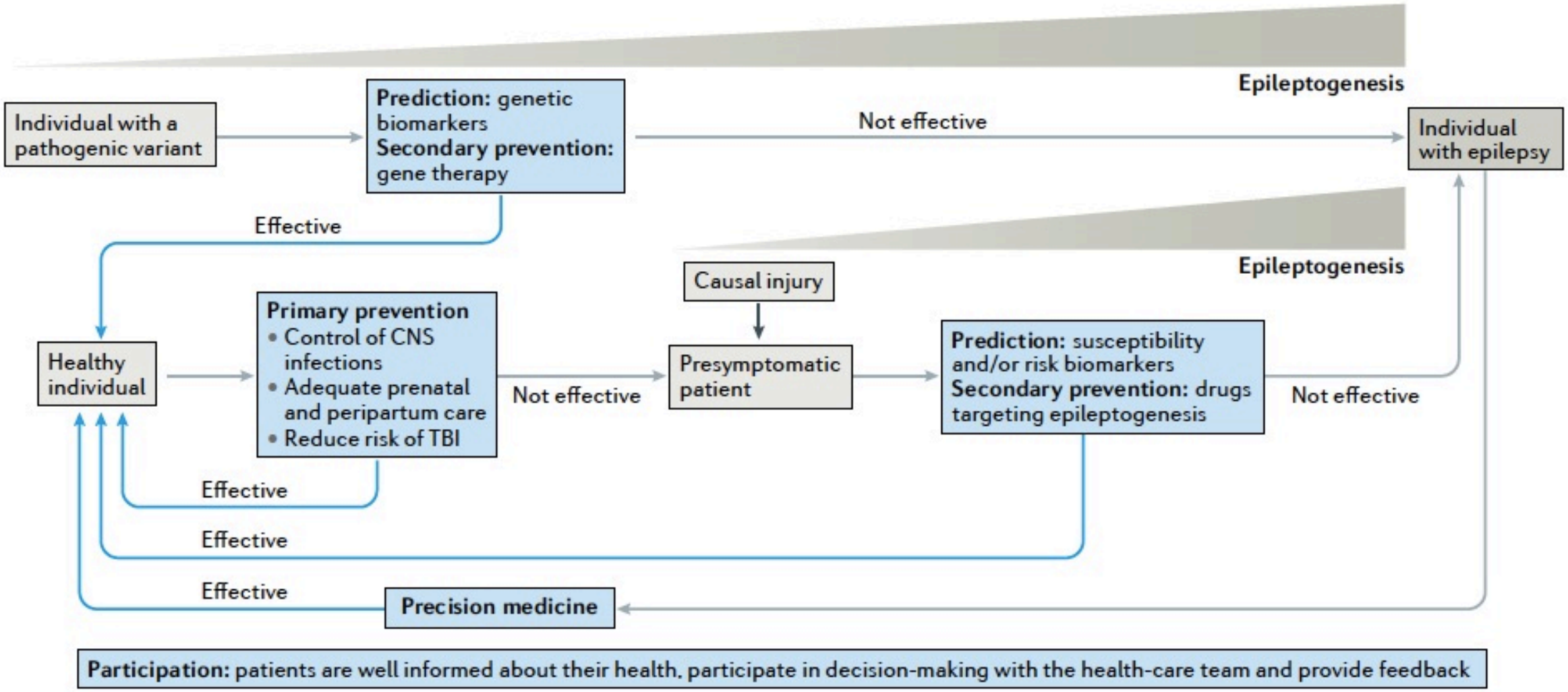
Proactive Approach
‘4P-medicine’

- Personalized
- Preventive
- Predictive
- Participatory





P4-Medicine Approach



Nabbout R, Kuchenbuch M, Nat Rev Neurol 2020

Precision Medicine in Clinical Practice

- First, do no harm
- Do nat fall behind
- Evidence-based individual strategies
- Gene therapy
- From early to ‘preventive’ therapies

Nabbout R, Kuchenbuch M, Nat Rev Neurol 2020

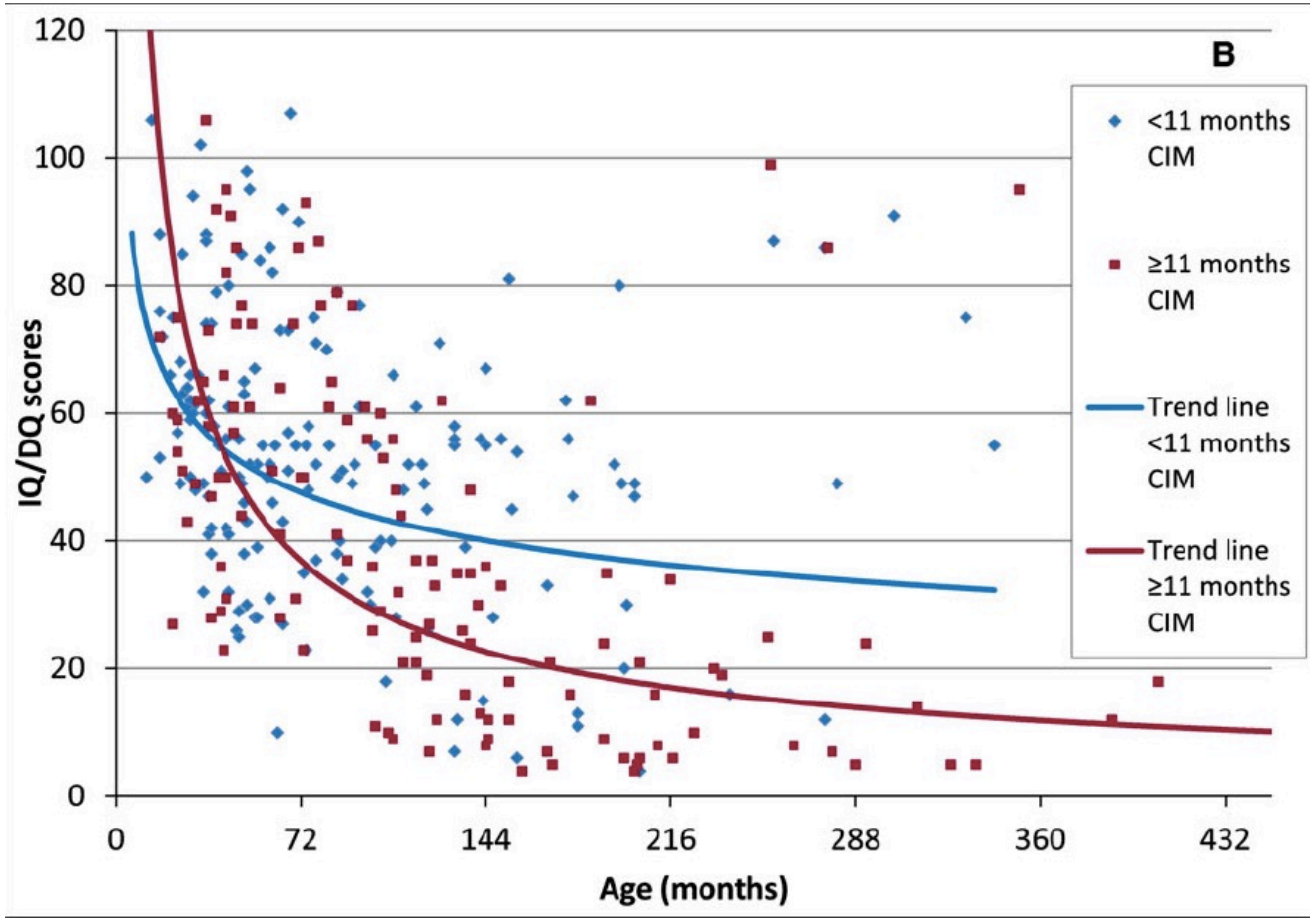
Precision Medicine in Clinical Practice

- **First, do no harm**:
  - Treatment with sodium channel blockers medication in Dravet syndrome
    - Increase in seizure frequency and duration
    - Negative effect on cognitive outcomes
- Do nat fall behind
- Evidence-based individual strategies
- Gene therapy
- From early to ‘preventive’ therapies

Nabbout R, Kuchenbuch M, Nat Rev Neurol 2020

Impact of Contraindicated ASM

- 164 Dutch children with SCN1A-relatd seizures (116 with Dravet syndrome)
- 86% had been exposed to contraindicated ASM (CBZ, OXC, PHT, LTG, VGB)
- Correlated duration of contraindicated ASMs use in the first 5 years of life and cognition
- Longer duration of incorrect ASMs correlated with lower developmental quotient



de Lange IM, et al. Epilepsia 2018

Precision Medicine in Clinical Practice

- First, do no harm
- **Do nat fall behind**
  - Delays in initiating therapy are associated with a negative impact on outcomes in numerous epilepsies including infantile spasms
- Evidence-based individual strategies
- Gene therapy
- From early to ‘preventive’ therapies

Nabbout R, Kuchenbuch M, Nat Rev Neurol 2020

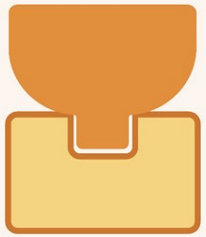
Precision Medicine in Clinical Practice

- First, do no harm
- Do nat fall behind
- **Evidence-based individual strategies**
  - Substitute therapies
  - Therapies that modify cell-signaling pathways
  - Function-based therapies
- Gene therapy
- From early to ‘preventive’ therapies

Nabbout R, Kuchenbuch M, Nat Rev Neurol 2020

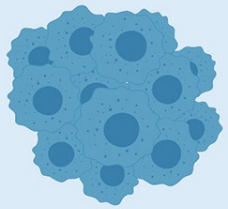
Etiology & Directed Therapeutics

SUPPLEMENTATION/RESTRICTION OF SUBSTRATES



SLC2A1	Ketogenic diet
SLC6A8	Creatine
SLC35A2	Galactose
ALDH7A1	Pyridoxine
PNPO	Pyridoxal 5-' phosphate (P5P)
PIG-	Pyridoxine or P5P
FOLR	Folinic acid
MOCS	c-PMP
TPP1	Cerliponase alfa
TRPM6	Magnesium sulfate

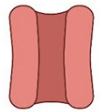
MODIFICATION OF SIGNALING PATHWAYS



DEPDC5
NPRL2
NPRL3
TSC1
TSC2

Rapamycin derivatives

CHANNELS/RECEPTORS-GUIDED POTENTIAL THERAPIES



Na	SCN1A, SCN2A, SCN8A	Management of Na channel blockers basing on function.	
K	KCNT1, KCNT2	GoF	Quinidine
	KCNQ2, KCNQ3	GoF	Na channel blockers
	KCNA2	GoF	Aminopiridine
Ca	CACNA1A	GoF	ETX/LTG
GTMT	GRIN2A GRIN2B GRIN2D	GoF	Memantine
ACh-R	CHRNA2 CHRNA4 CHRNB2	LoF	Nicotine
cAMP	HCN1	GoF	Ketamine
		LoF	LTG/GBP

OTHER POTENTIAL THERAPEUTIC APPROACHES

SCN1A	STP/CBD/FFA
PCDH19	LEV/CLB
CDKL5	Ganaxolone
STXBP1	LEV
SLC6A1	VPA + LTG
PRRT2	Na blockers
InvDup 15	Na blockers

Beltran-Corbellini A et al. Front Neurol 2022

GLUT1DS

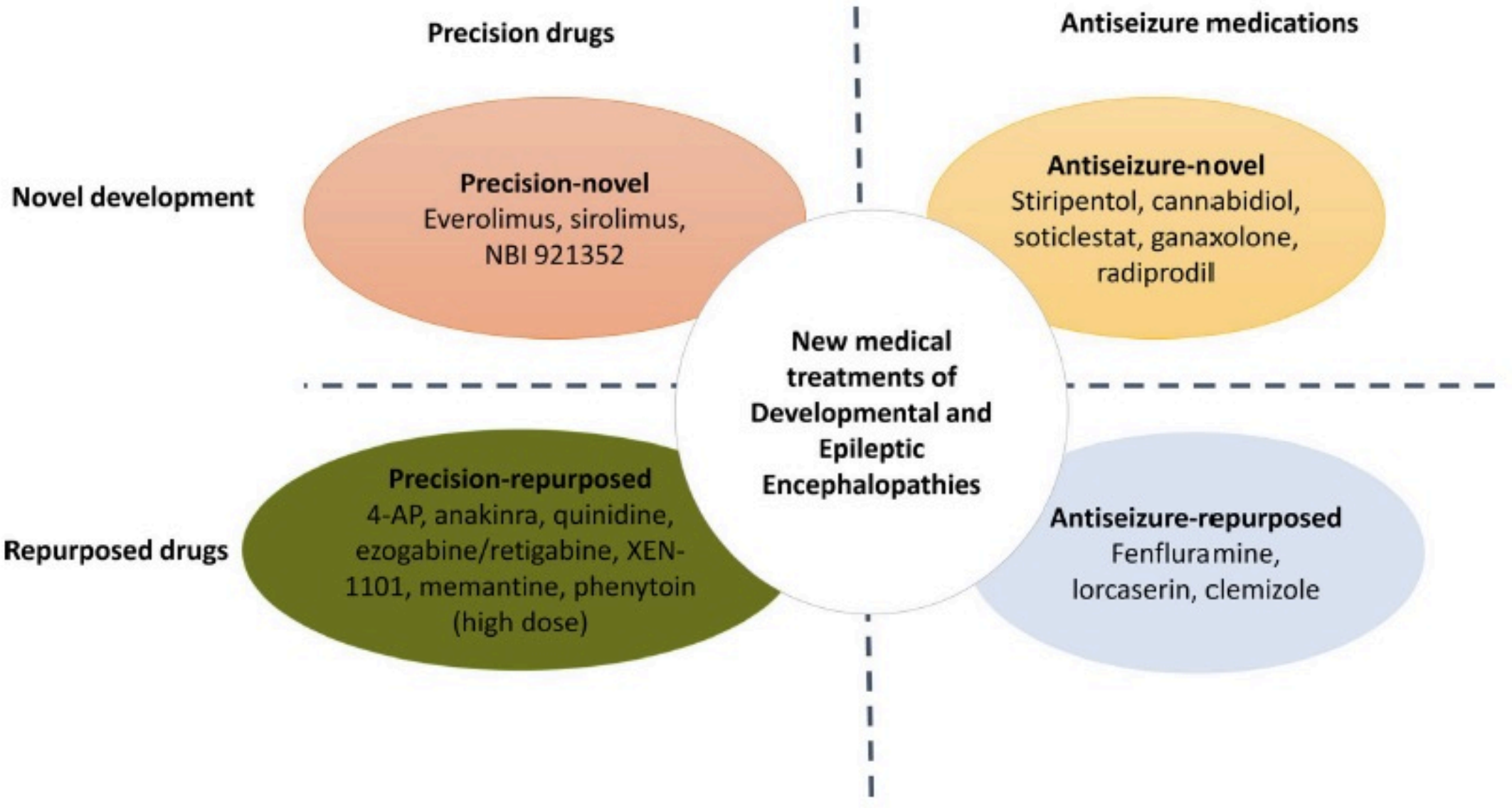
- Cerebral “energy crisis”
- Symptoms develop in an age-specific pattern
- Infancy
  - Early onset absence epilepsy (< 4 yo), Myoclonic-atonic seizures
  - Paroxysmal eye-head movement
- Movement disorders: paroxysmal or persistent
  - Ataxia, spastic, dystonia
- Acquired microcephaly and cogntive impairment
- LP shows hypoglycorrachia (< 40 mg/dL)
- SLC2A1 mutation or deletion/duplication
- Early ketogenic diet treatment: better intellectual outcomes

Klepper J, et al. Epilepsia Open 2020

Dravet Syndrome

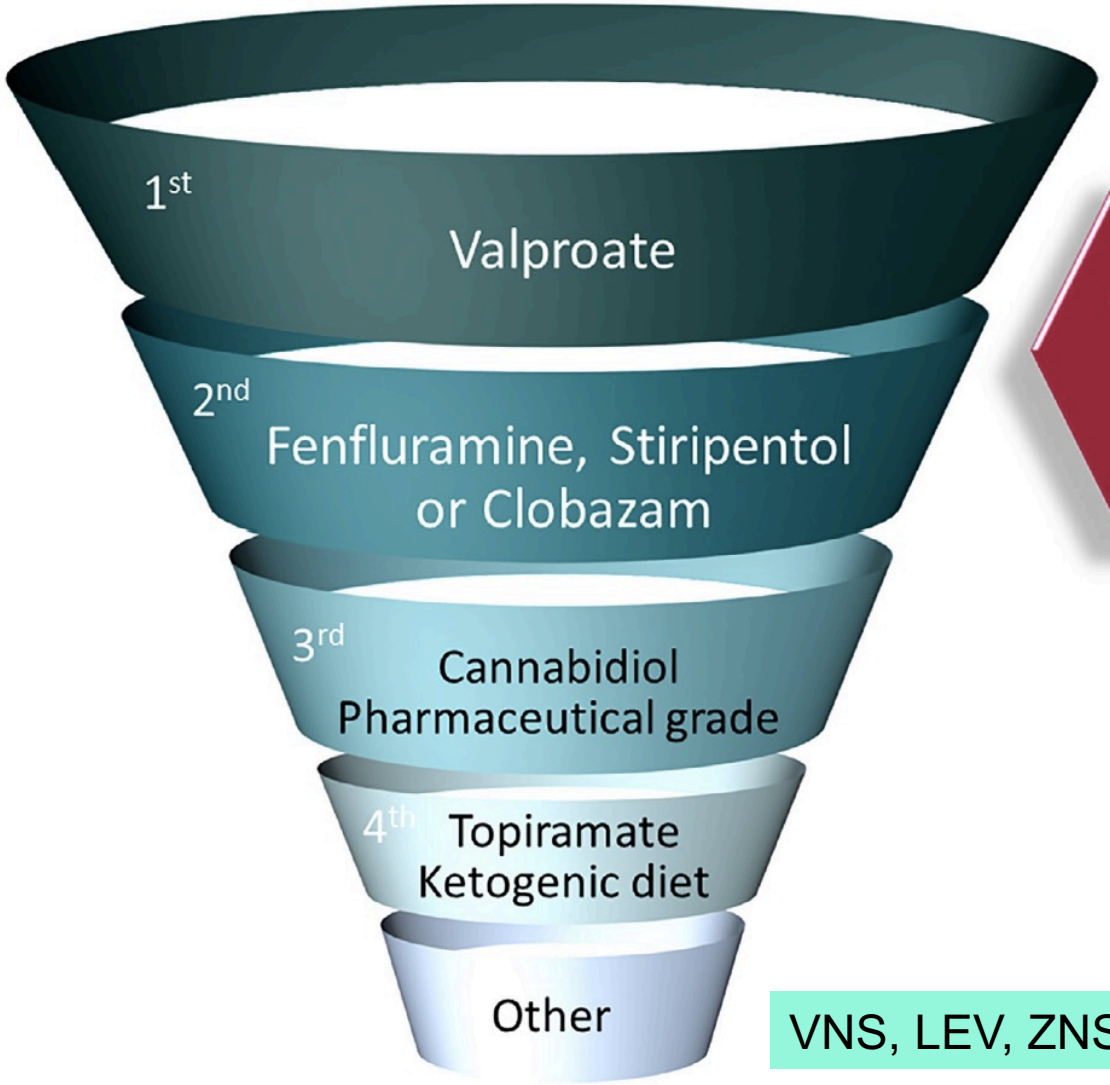
- Normal growth and development as infants
- Seizures present in the first year of life
  - Initially, GTC often prolonged, associated with fever
  - Prolonged hemiclonic seizures
- Evolution to myoclonic seizures, atypical absence seizures, generalized tonic-clonic seizures with/without fever, and complex partial seizures, usually with secondary generalization
- Concomitant psychomotor decline
- Unfavorable outcome due to ongoing seizures
- Genetic etiology: 70%-80% have **SCN1A** mutations

New Medical Treatments for DEE



Landmark J et al. Epilepsia 2020

Treatment Algorithm for Dravet Syndrome



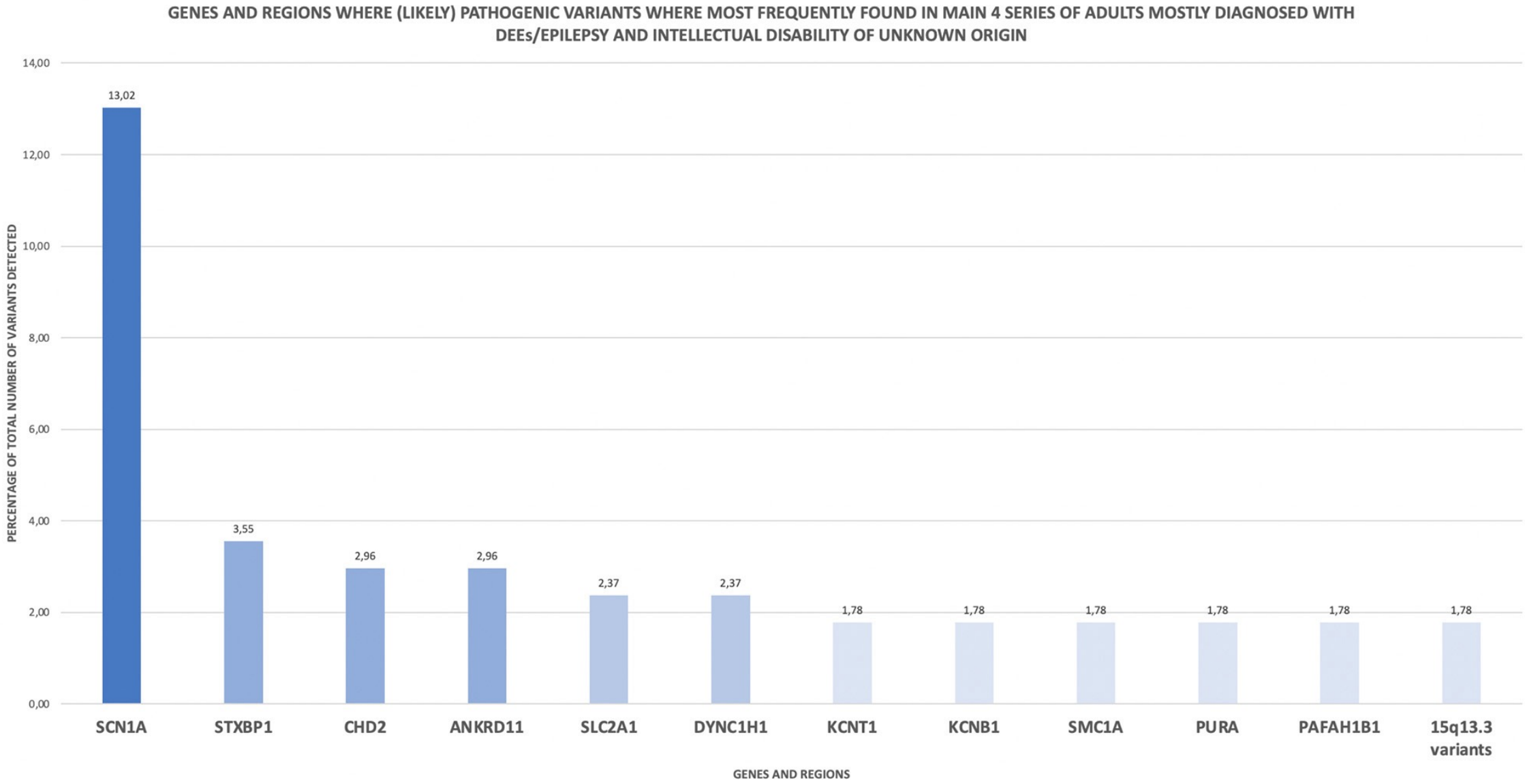
AVOID
Carbamazepine,
Oxcarbazepine
Lamotrigine,
Phenytoin**

PHT may be helpful for SE

VNS, LEV, ZNS, CNZ

Wirrell EC, et al. Epilepsia 2022

Most Frequent Genetic Epilepsies in Adults



Beltran-Corbellini A et al. Front Neurol 2022

Dravet Syndrome in Adults

- Epilepsy severity decreases from childhood to adults
- Seizures persist in adolescents (76%) and adults (80%), mostly nocturnal GTCs and in cluster
- Gait abnormaliites: ‘Crouch gait’
- Parkinsonian features without resting tremor
- Intellectual disability and language impairment

Darra F, et al. Epilepsia 2019, Selsavarah A, Seizure 2021

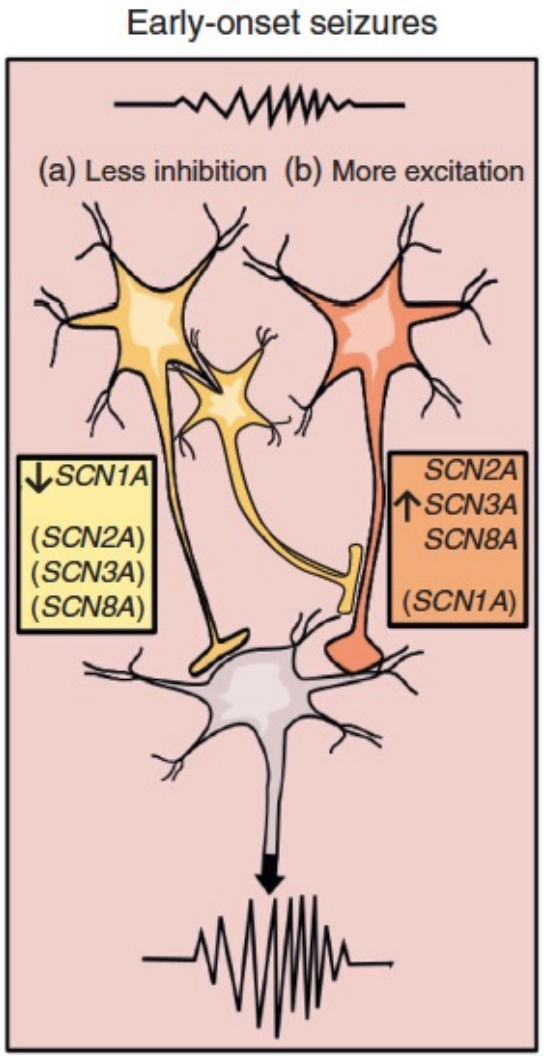
Precision Medicine in Clinical Practice

- First, do no harm
- Do nat fall behind
- Evidence-based individual strategies
- **Gene therapy:** antisense oligonucleotides (ASO)
- From early to ‘preventive’ therapies

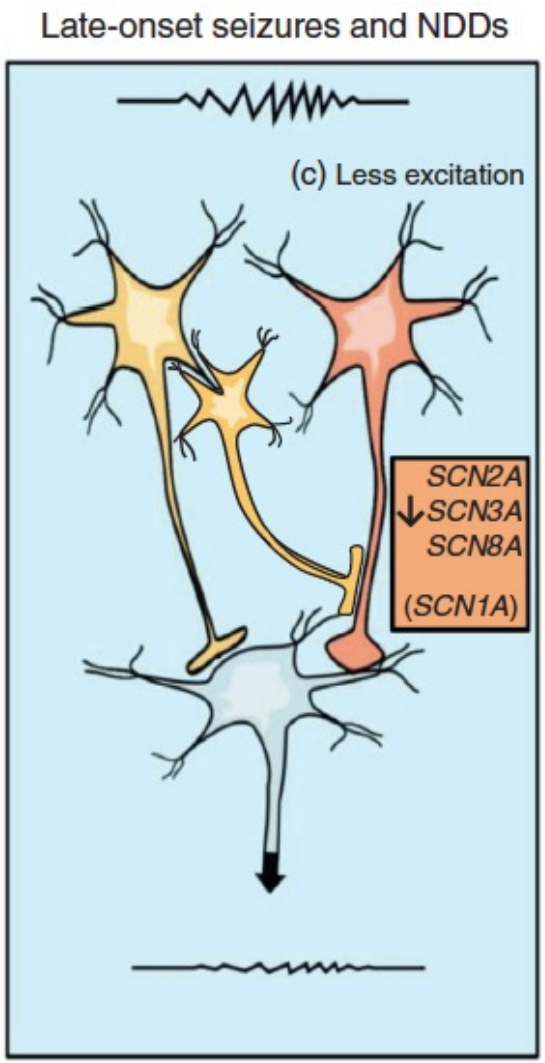
Nabbout R, Kuchenbuch M, Nat Rev Neurol 2020

Sodium Channel Epilepsies and Neurodevelopmental disorders

Loss of function (LOF): Avoid sodium channel blockers (SCB)



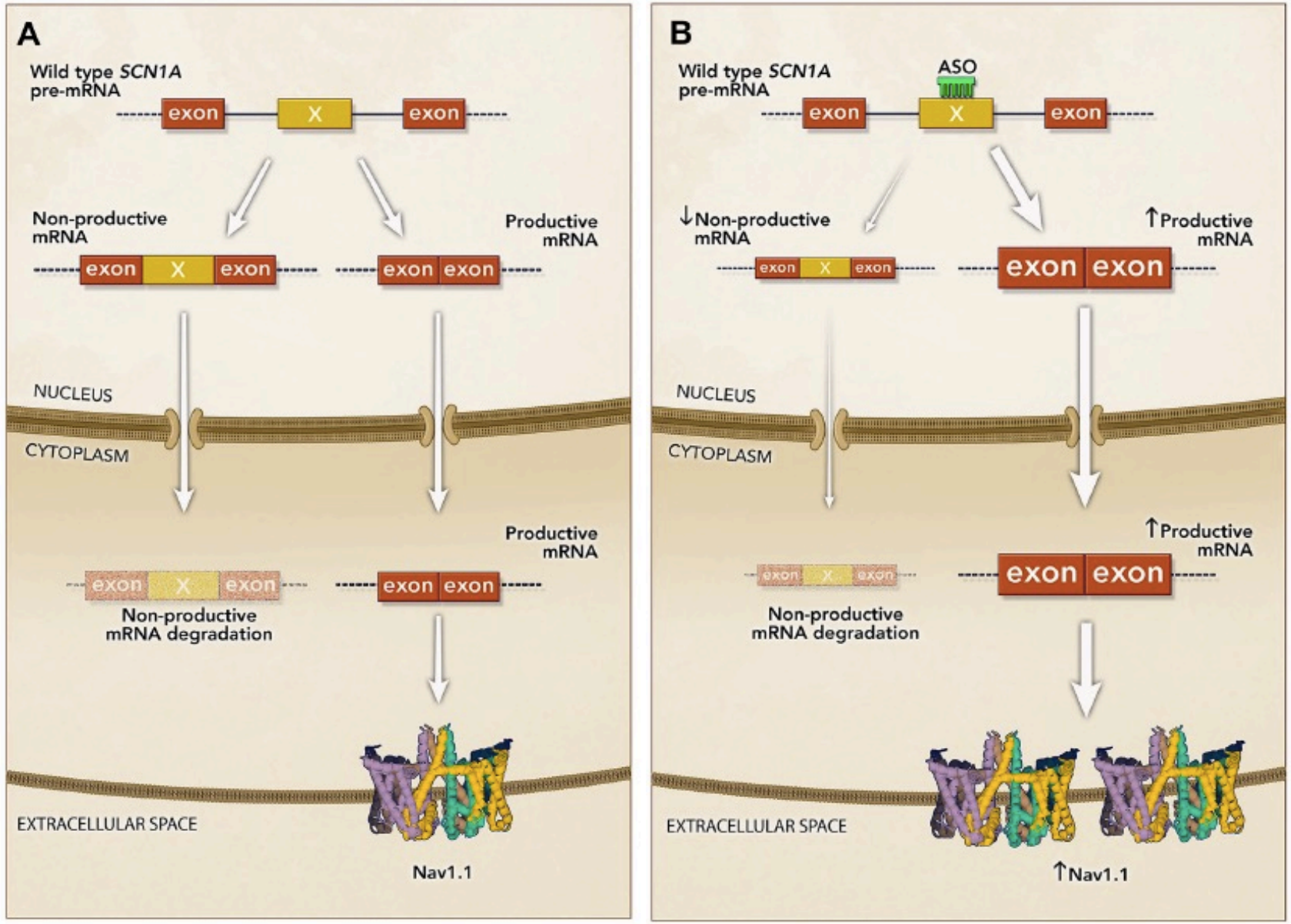
Gain of function (GOF): SCB is effective



Loss of function (LOF): SCB is not effective

Branklaus A & Lal D, Dev Med Child Neurol 2020

Steric Blocking ASO: STK-001
Targeted augmentation of nuclear gene output (TANGO)



Limited to SCN1A

Nav1.1 haploinsufficiency

Contraindicated to missense SCN1A

Isom LL & Knupp KG, Neurotherapeutics 2021

STK-001 as Disease-Modifying Medicine for Dravet Syndrome

Key Safety Findings of Phase 1/2a study

- At the time of the analyses, 81 patients had been treated with STK-001.
- STK-001 was generally well-tolerated across the Phase 1/2a and OLE studies.
- In the Phase 1/2a studies:
  - 30% (24/81) of patients experienced a treatment-emergent adverse event (TEAE) that was related to study drug. The most common were CSF protein elevations and procedural vomiting; and
  - 22% (18/81) of patients had a treatment-emergent serious adverse event. These events were assessed as unrelated to study drug except for the previously reported case of one patient who experienced Suspected Unexpected Serious Adverse Reactions (SUSARs).
- A greater incidence of CSF protein elevation was observed in the OLEs. 74% (50/68) of patients in the OLEs had at least 1 CSF protein value >50 mg/dL. No clinical manifestations have been observed in these patients.
- Across the studies, one patient discontinued treatment due to study drug. As previously reported, this patient discontinued treatment in the OLE due to elevated CSF protein.

https://investor.stoketherapeutics.com/news-releases/news-release-details/stoke-therapeutics-announces-landmark-new-data-support-potential

STK-001 as Disease-Modifying Medicine for Dravet Syndrome

Observed reductions in convulsive seizure frequency in the Phase 1/2a studies

Median % Reduction From Baseline In Convulsive Seizure Frequency	70 mg (1 Dose, N=8)	70 mg (2 Or 3 Doses, N=11)
At 3 Months After Last Dose	43% (N=8)	85% (N=10†)
At 6 Months After Last Dose	57% (N=7*)	74% (N=9†)

Ongoing studies for STK-001

US studies (age 2 – 18 years)

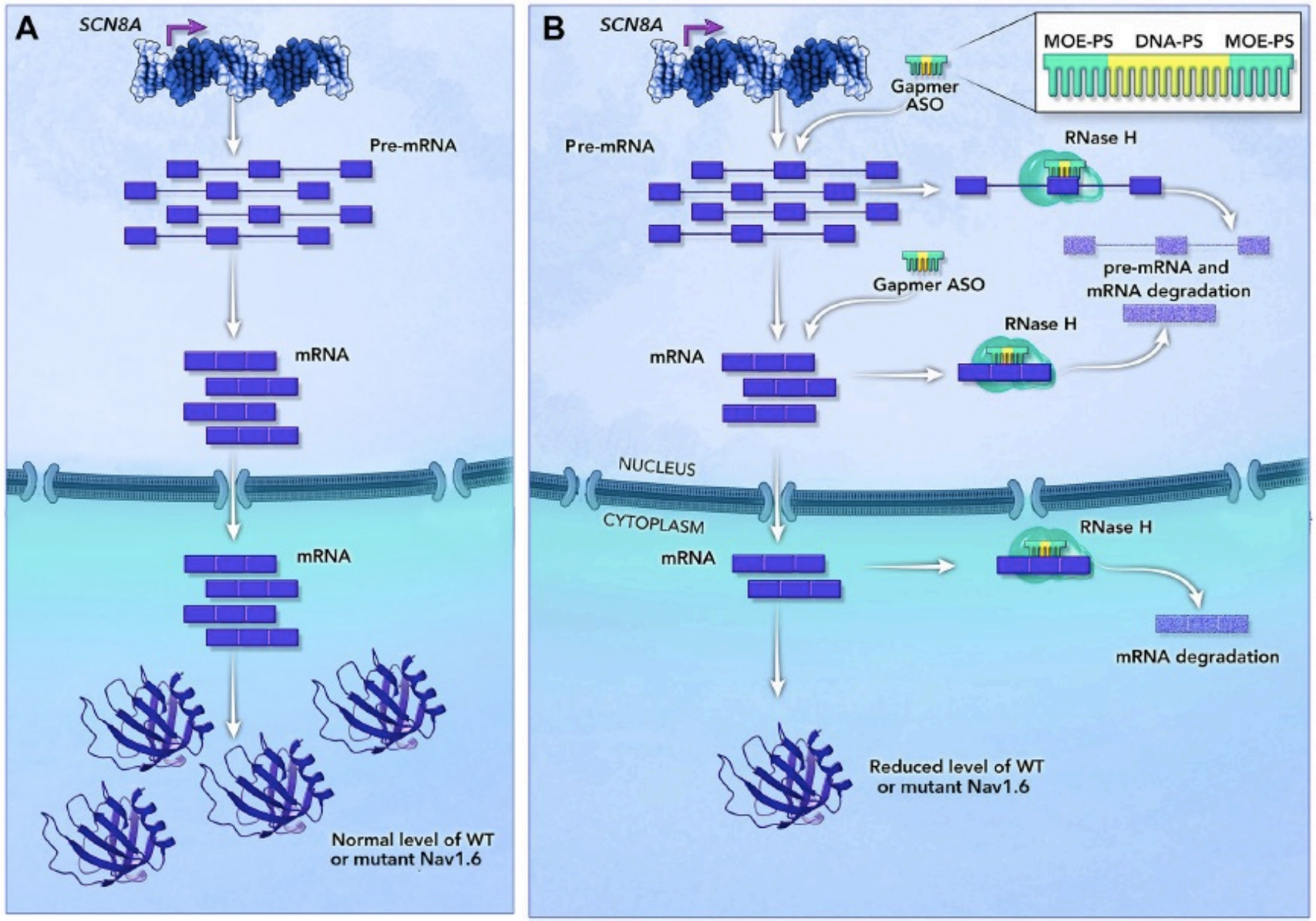
- **MONARCH**: phase 1/2a study – safety, tolerability, and PK of STK-001
- **SWALLOWTAIL:** Open-label extension study – long-term safety & tolerability

UK studies(age 2 – 18 years)

- **ADMIRAL:** phase 1/2a study – safety, tolerability, and PK of STK-001
- **LONGWING:** Open-label extension study – long-term safety & tolerability

https://investor.stoketherapeutics.com/news-releases/news-release-details/stoke-therapeutics-announces-landmark-new-data-support-potential

Mechanism of Action of SCN8A Gamper



Isom LL & Knupp KG,
Neurotherapeutics 2021

Precision Medicine in Clinical Practice

- First, do no harm
- Do nat fall behind
- Evidence-based individual strategies
- Gene therapy
- **From early to ‘preventive’ therapies**

Nabbout R, Kuchenbuch M, Nat Rev Neurol 2020

Prevention of Epilepsy in 79 Infants with TSC: EPISTOP Trial

- 25 had preventive treatment at time of abnormal EEG (PTx)
- 25 had NO preventive treatment at time of abnormal EEG (CTx)
- 22 had seizure prior to detection of interictal epileptiform activity (EA)
- 7 never had EA or seizures, and had no treatment
- Treatment: VGB 100-150 mg/kg/day until 2 years

Kotulska K, et al. Ann Neurol 2021

Prevention of Epilepsy in 79 Infants with TSC: EPISTOP Trial

Primary outcome

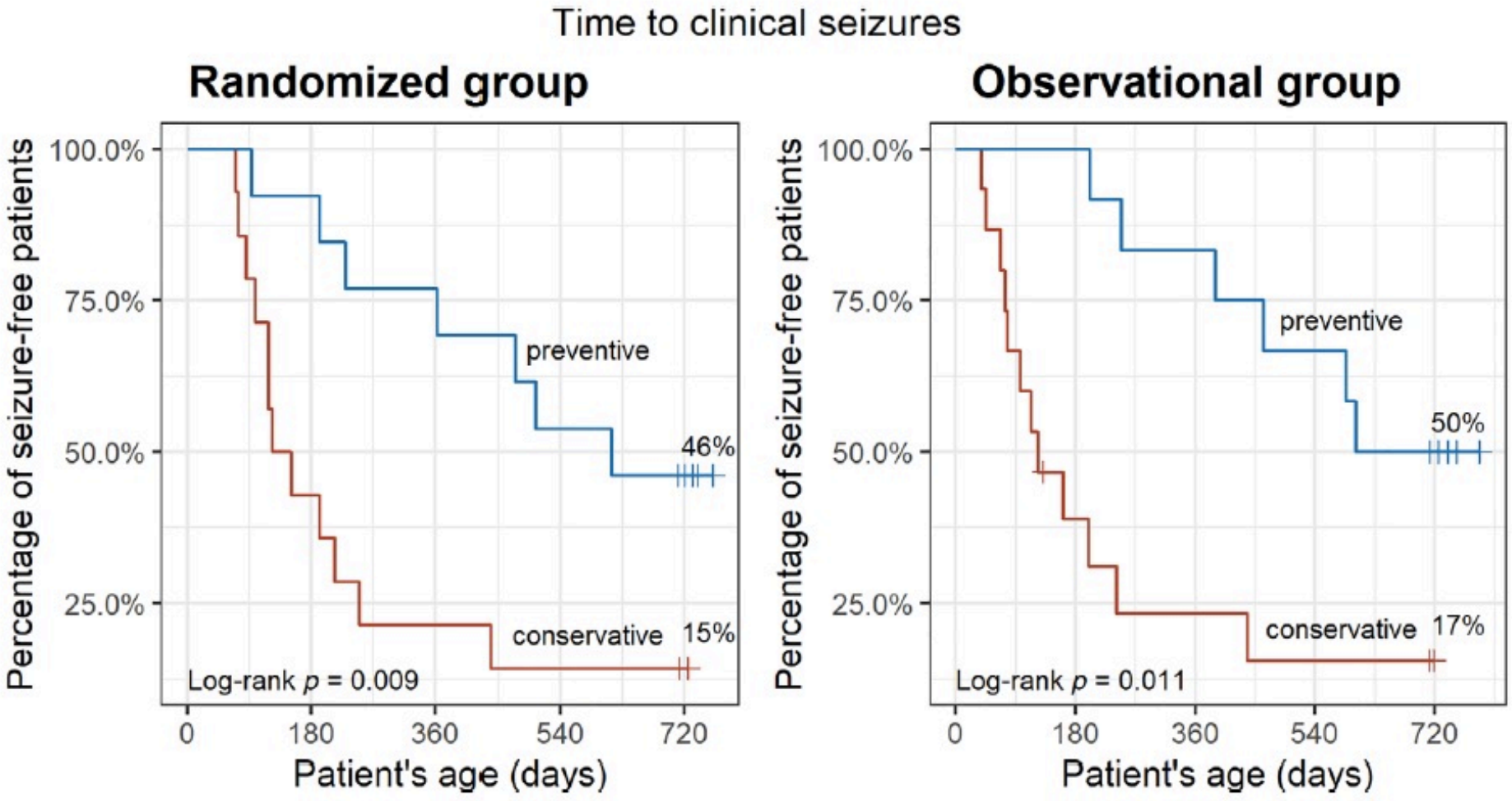
- Time to first clinical seizure in PTx was 614 days vs 125 days in CTx
- Time to IED to first seizure in PTx was 561 days vs 61 days in CTx

Secondary outcomes (at 2 years)

- DRE in PTx vs CTx [28% vs 64%, OR = 0.23 (0.06-0.83)]
- Infantile spasms [0 vs 40%, OR = 0 (0, 0.33)]
- Neurodevelopmental delay [25% vs 41%, OR = 0.55 (0.12, 2,27)]
- Autisms [32% vs 18%, OR = 2.06 (0.43, 11.58)]

Kotulska K, et al. Ann Neurol 2021

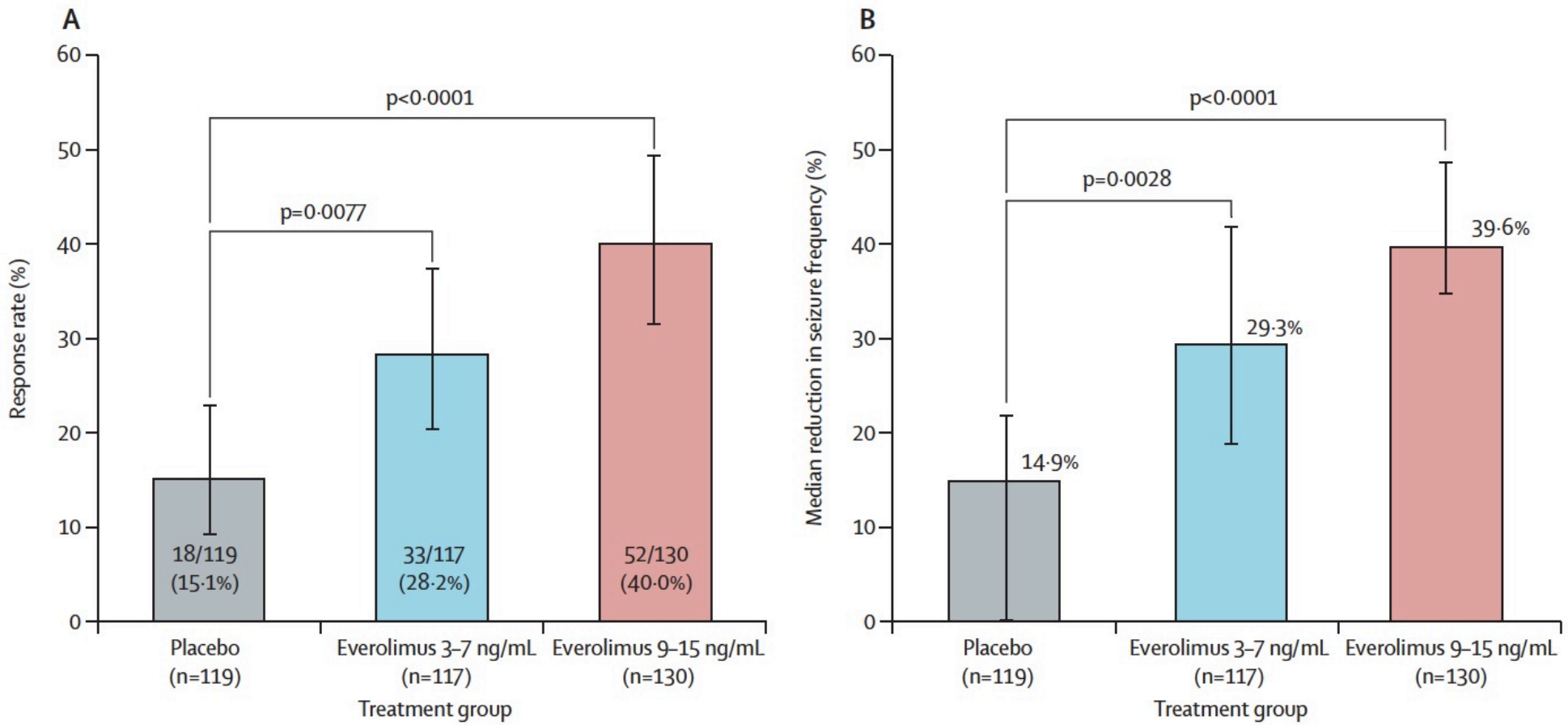
Prevention of Epilepsy in 79 Infants with TSC: EPISTOP Trial



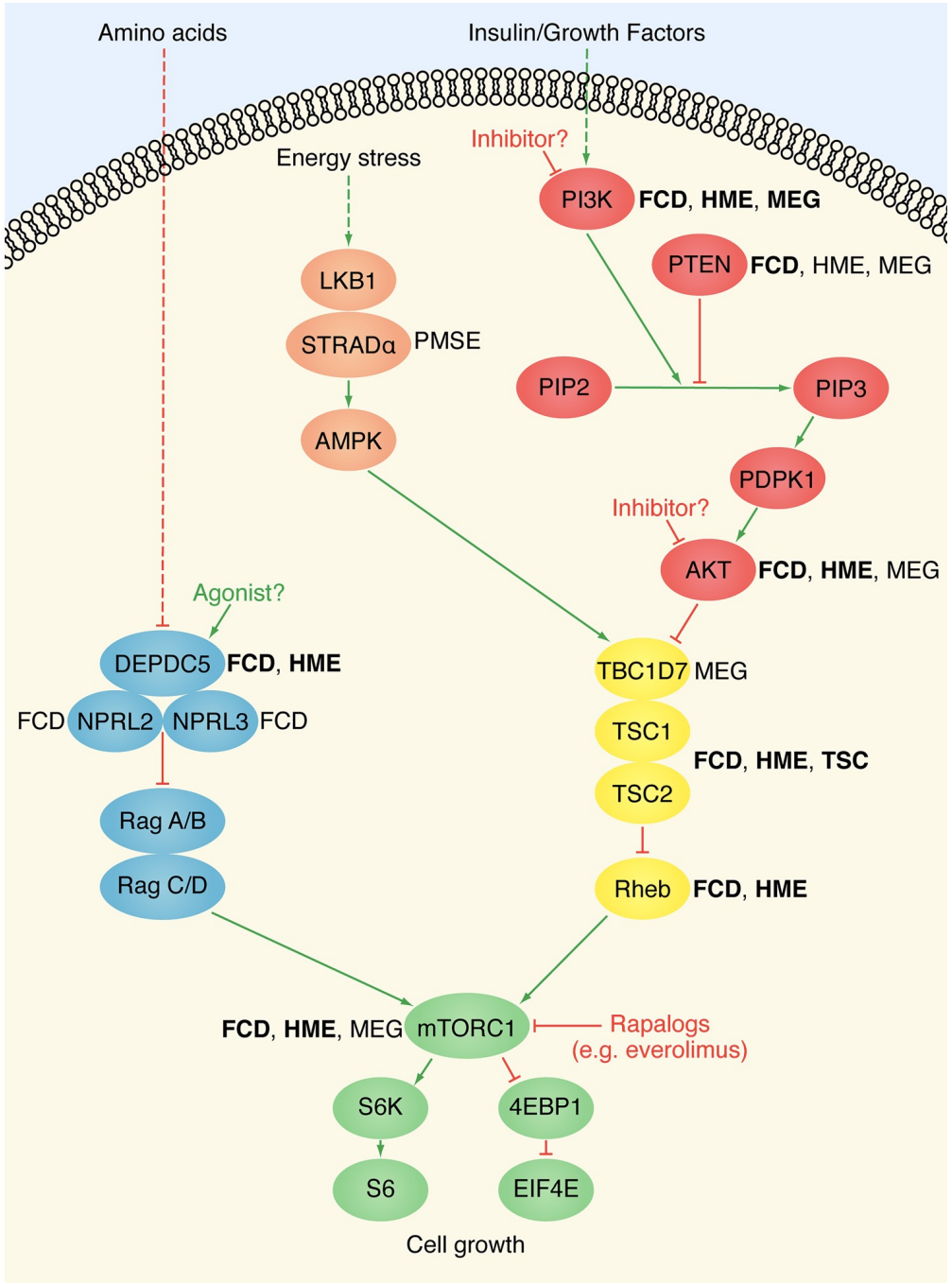
Preventive group were 3 times more likely to remain free of clinical seizures

Kotulska K, et al. Ann Neurol 2021

Everolimus for Treatment-Resistant Focal Seizures in TSC (EXIST-3)



French JA,et al. Lancet Neurol 2016

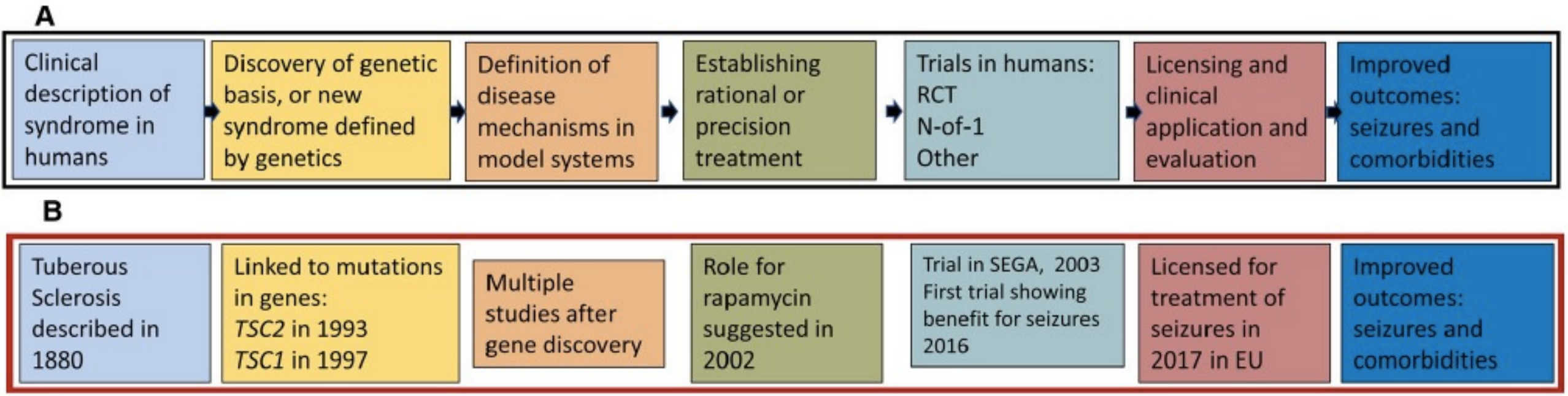


mTORpathies

- TSC, hemimegalencephaly (HME), FCD, polyhydramnios megalencephaly and symptomatic epilepsy (PMSE)
- VGB decreased activation of mTOR pathway
- Everolimus is approved for DRE associated with TSC
- mTOR inhibitors may need to start early during epileptogenesis in epilepsy related to MCDs

D'Gama AM & Poduri A, Neurotherapeutics 2021

Typical Current PM Scenario

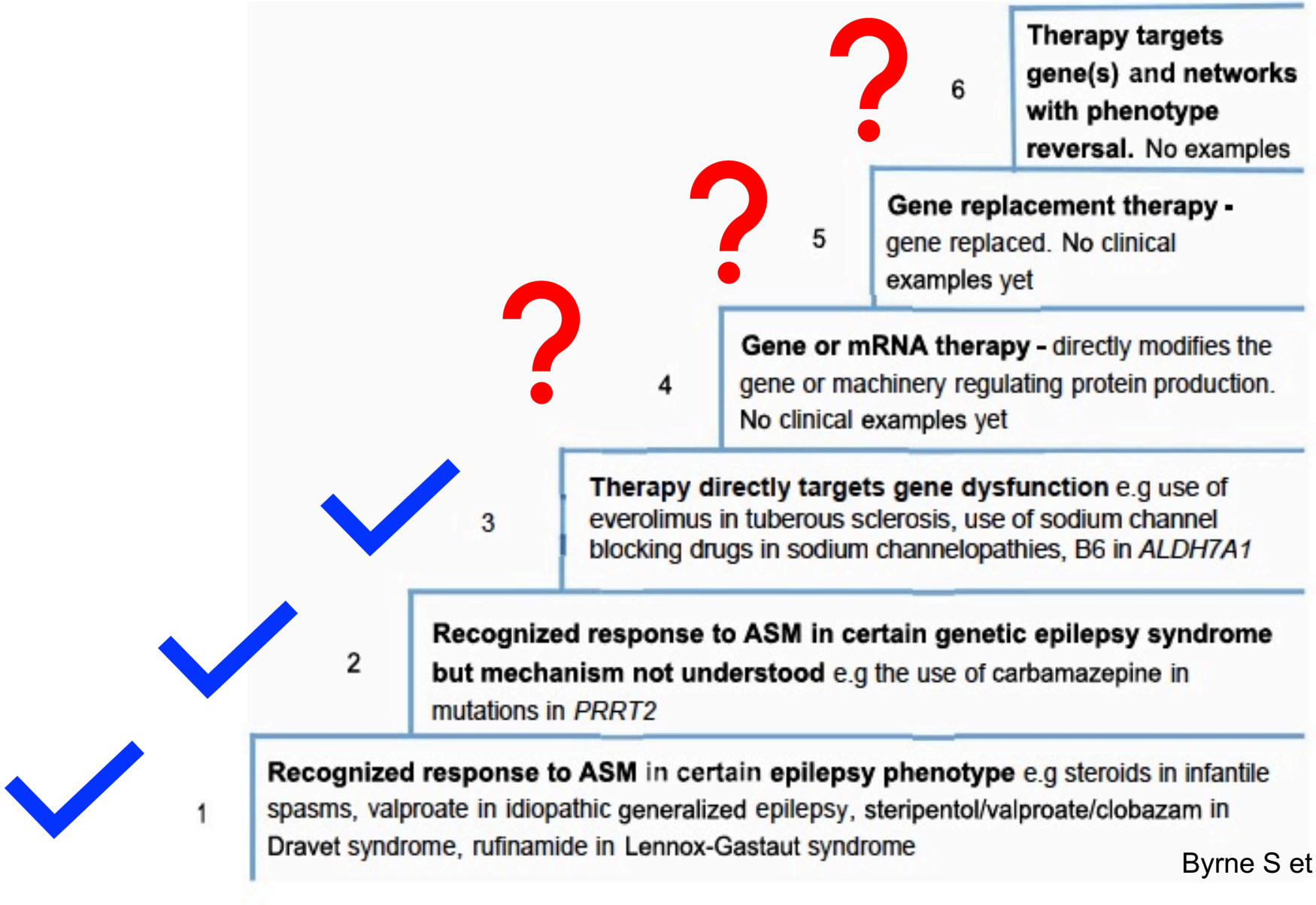


Sisodiya SM Epilepsia 2020

Challenges of PM

- Complexity of genotype-phenotype correlation
- Unequal access
- Genetic discovery is outpacing clinical knowledge of pathogenesis and clinical course
- Further validation & application of preclinical models
- Infrastructure & common standards of gene-based therapies
- Traditional RCT not feasible with rare diseases

Is Precision Medicine the Answer to DEE?



Byrne S et al. Dev Med Child Neurol 2021

Conclusions

- Advnances in genetics have led to the development of diagnostic biomarkers for epilepsy
- Targeted therapies and gene therapy are components of PM which belongs to ’P4’ medicine
- Primary and secondary prevention of epilepsy is becoming a reality in humans particularly in the case of monogenic epilepsy
- Systematic epilepsy PM pipeline is further needed with collaboration of expert teams of clinicians, scientists, patients, and policy makers
- “Time is brain and we’ve lost too much of both”


Thank You For Your Attention